DETAILED ACTION

Status of the Application

[1] Claims 1-40, 42-44, and 46-65 are pending in the application.

[2] Applicant's amendment to the claims, filed on 11/5/09, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 11/5/09, is acknowledged.

[4] Receipt of an information disclosure statement, filed on 5/26/09, is acknowledged.

[5] Applicant's remarks filed on 11/5/09 in response to the non-final Office action mailed on 12/26/08 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Rejections and/or objections previously applied to claims 41 and 45 are withdrawn solely in view of the instant amendment, which cancels these claims.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[7] Claims 1-40, 42-44, and 46-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made without traverse in the replies filed on 5/16/08 and 10/1/08.

Information Disclosure Statement

[8] The information disclosure statement (IDS) submitted on 5/26/09 was filed after the mailing date of the first Office action on the merits on 12/26/08. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification/Informalities

[9] The objection to the title of the invention as not being descriptive is withdrawn in view of the instant amendment to the specification to amend the title to read ---Method for Decreasing a Protein-Protein Interaction Between an E3 Ubiquitin Ligase and an E3 Ubiquitin Ligase Substrate---.

Claim Rejections - 35 USC § 112, Second Paragraph

[10] New claims 55-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by the instant claim amendment.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board

of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 55 (claims 57-65 dependent therefrom) recites the broad recitation “an E3 ubiquitin ligase” in line 3, and the claim also recites “an anergy associated E3 ubiquitin ligase” in lines 1-2 which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 112, First Paragraph

[11] New claims 55-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection and is necessitated by the instant claim amendment. The analysis given to the claims is similar to the analysis set forth in Example 17, Claim 1, of the Written Description Training Materials, Revision 1, March 25, 2008, which is electronically available via the web address http://www.uspto.gov/web/menu/written.pdf.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

CLAIM INTERPRETATION: Claim 55 (claims 62-65 dependent therefrom) is drawn to a method for decreasing protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate by contacting the E3 ubiquitin ligase with a genus of ligase-binding antibodies or fragments thereof…to thereby decrease protein-protein interaction between the ligase and E3 ubiquitin ligase substrate. Since the protein-protein interaction is decreased by the presence of the ligase-binding antibody, the genus of antibodies is interpreted as encompassing the function of decreasing protein-protein interaction between the ligase and E3 ubiquitin ligase substrate. Claim 56 limits the E3 ubiquitin ligase to Aip4 and the substrate to PKCθ. Claims 57-61 limit the antibody.

MPEP 2163.II.A.2.(a).i) states, "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed

correlation between structure and function, and the method of making the claimed invention".

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification fails to disclose the reduction to practice of even a single representative species of the genus of "agents". While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus".

In order to achieve a decrease in protein-protein interaction, a ligase-binding antibody that decreases protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate is required. The specification does not describe an actual reduction to practice of a method of decreasing protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate by contacting the E3 ubiquitin ligase with a ligase-binding antibody to thereby decrease protein-protein interaction. The specification also does not describe the complete structure of a ligase-binding antibody that decreases protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate. Further, the specification does not describe the partial structures, or physical properties, or chemical properties of a ligase-binding antibody that decreases protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate. While the prior art discloses E3 ubiquitin ligases and substrates thereof, *e.g.,* Aip4 and PKCθ, the specification does not describe any correlation between the sequences of E3 ubiquitin ligases and substrates thereof and the structure of a ligase-binding antibody that decreases protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate. The specification describes methods of screening for a ligase-binding antibody that decreases protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate; however, there is no information regarding what structural features would likely be associated with the function of decreasing protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate. In this regard, Pray et al. (*Drug Resistance Updates* 5:249-258, 2002) acknowledges that in drug discovery centered

around E3 ubiquitin ligases, “a large array of interactions must be taken into account” and while “each of these interactions...is a potential target for...inhibition", it is "daunting in terms of developing accurate structure-activity relationships" (p. 256, column 1, top). Thus, the specification does not disclose a correlation between decreasing protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate and the structure of a putative antibody having that function.

Given the lack of description of even a single representative species of the recited genus of ligase-binding antibodies that decrease protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

RESPONSE TO ARGUMENT: To the extent applicant's remarks address the instant rejection, they are addressed below. Beginning at p. 15 of the instant remarks, applicant argues the written description rejection is obviated by amendment to limit the "agents" to a ligase-binding antibody, where the specification discloses the use of such antibodies and fragments thereof at pp. 48-51 of the specification. According to applicant, in view of this disclosure, a skilled artisan would recognize that applicant was in possession of the claimed invention at the time of filing.

Applicant’s argument is not found persuasive. Pages 48-51 of the specification do not appear to disclose a reduction to practice of the claimed method, nor does the

noted disclosure appear to disclose a reduction to practice of even a single ligase-binding antibody that decreases protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate, much less a sufficient number of species that are representative of the entire genus of ligase-binding antibodies that decrease protein-protein interaction between all E3 ubiquitin ligases and an E3 ubiquitin ligase substrate. Because the specification fails to disclose a representative species of an antibody that decreases protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate, it appears applicant takes the position that possession of such an antibody is shown because one can make and test for such an antibody, however, according to the Court in *University of Rochester v. G.D. Searle & Co.*, 71 USPQ2d 1545 (Fed. Cir. 2004), "[a]n adequate written description of a DNA . . . 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention."

[12] New claims 55-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is necessitated by the instant claim amendment.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining

whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors considered to be most relevant to the instant rejection are addressed in detail below.

(A) The breadth of the claims: Claim 55 is drawn to a method for decreasing protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate by contacting the E3 ubiquitin ligase with a ligase-binding antibody or fragment thereof…to thereby decrease protein-protein interaction between the ligase and E3 ubiquitin ligase substrate. Since the protein-protein interaction is decreased by the presence of the ligase-binding antibody, the antibody or fragment thereof is interpreted as encompassing the function of decreasing protein-protein interaction between the ligase and E3 ubiquitin ligase substrate. Claim 56 limits the E3 ubiquitin ligase to Aip4 and the substrate to PKCθ. Claims 57-61 limit the antibody. Claim 62 requires the E3 ubiquitin ligase and an E3 ubiquitin ligase substrate to be “provided within a cell”; claim 63 limits the cell to a human cell; claim 64 requires the cell to be within a "patient"; and claim 65 requires the patient to be a human patient.

(B) The nature of the invention: The nature of the invention appears to be in the finding that E3 ubiquitin ligases mediate degradation of calcium and calcineurin

signaling molecules, which results in anergy (antigen unresponsiveness) in T cells (see, *e.g.,* specification at pp. 72-75).

(C) The state of the prior art; (D) The level of one of ordinary skill; and (E) The level of predictability in the art: According to MPEP 2164.03, "…what is known in the art provides evidence as to the question of predictability." At the time of the invention, the prior art recognized E3 ubiquitin ligases as a therapeutic target as shown by Pray et al. (*Drug Resistance Updates* 5:249-258, 2002). Even so, Pray et al. recognizes challenges in targeting E3 ubiquitin ligases as therapeutic targets, noting a factor in the complexity of identifying drugs that target E3 ubiquitin ligases is "the fact that many E3 ligases are themselves multi-component complexes…a large array of interactions must be taken into account" and that the development of accurate structure-activity relationships between E3 ubiquitin ligases and their substrates is "daunting" (p. 256, column 1, top). However, while E3 ubiquitin ligases were identified as potential therapeutic targets, the prior art does not appear to disclose a ligase-binding antibody or fragment thereof that, when contacted with an E3 ubiquitin ligase, achieves a decrease in protein-protein interaction between the ligase and an E3 ubiquitin ligase substrate.

(F) The amount of direction provided by the inventor and (G) The existence of working examples: The specification fails to disclose even a single working example of a ligase-binding antibody or fragment thereof that, when contacted with an E3 ubiquitin ligase, achieves a decrease in protein-protein interaction between the ligase and an E3 ubiquitin ligase substrate or guidance regarding the expectation of obtaining such an antibody. Although MPEP 2164.02 acknowledges that a working example is not

required, "Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art". The specification also fails to provide guidance regarding decreasing protein-protein interaction in a human patient.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of making an antibody were known at the time of the invention, there is no way to determine the quantity of experimentation required because the specification fails to disclose an antibody that has the activity of decreasing protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate and fails to provide a reasonable expectation that such an antibody can be made.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high level of unpredictability, undue experimentation would be necessary for a skilled artisan to make and use the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

RESPONSE TO ARGUMENT: To the extent applicant's remarks address the instant rejection, they are addressed below. Beginning at p. 16 of the instant remarks, applicant argues the enablement rejection is obviated by amendment to limit the "agents" to a ligase-binding antibody, the recitation of the target, and the specification's disclosure at pp. 45 and 47-54, one of skill in the art would be able to produce antibodies that decrease protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate without undue experimentation.

Applicant's argument is not found persuasive. Pages 45 and 47-54 of the specification do not appear to disclose a reduction to practice of the claimed method, nor does the noted disclosure appear to disclose a reduction to practice of a ligase-binding antibody that decreases protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate. Because the specification fails to disclose a working example of an antibody that decreases protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate, it appears applicant takes the position that the specification enables such an antibody and thus methods of using the antibody because one can make and test for such an antibody using routine techniques.

According to MPEP 2164.01(b), "[a] key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available…The Court in *In re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain

chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981). In this case, the specification and prior art fail to disclose even a single antibody that binds to a particular E3 ubiquitin ligase and that has the function of decreasing protein-protein interaction between a particular E3 ubiquitin ligase and its corresponding substrate, much less *all* antibodies that have the function of decreasing protein-protein interaction between all E3 ubiquitin ligases and their corresponding substrates. Moreover, the specification and prior art further fail to provide a reasonable expectation that such an antibody can be made or isolated using known techniques. As such, the specification and prior art fail to enable an antibody that binds to an E3 ubiquitin ligase and that has the function of decreasing protein-protein interaction between an E3 ubiquitin ligase and an E3 ubiquitin ligase substrate and thus fail to enable the claimed method.

Conclusion

[13] Status of the claims:

- Claims 1-40, 42-44, and 46-65 are pending.
- Claims 1-40, 42-44, and 46-54 are withdrawn from consideration.
- Claims 55-65 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
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